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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/689,122	10/20/2003	Tabassum Naqvi	3817.14-1	4234

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EXAMINER	
HAQ, SHAFIQUL	
ART UNIT	**PAPER NUMBER**
1641	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/689,122	NAQVI ET AL.	
	Examiner	Art Unit	
	Shafiqul Haq	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *9-17,20 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,18 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Election/Restrictions

1. Applicants' response filed October 30, 2006 to an election requirement in Office Action mailed October 5, 2006 is acknowledged and entered.

Applicants' election with traverse of Group I, claims 1-8 and 18-19, filed October 30, 2006 is acknowledged. Applicants' election of species "enzyme label" for detectable label is also acknowledged. Claims 2-6, 8 and 18-19 are readable on the elected species.

With respect to claim 12, the examiner agrees with the Applicants that amended claim 12, now dependent on claim 10, should properly be included in group III and thus group III includes claims 10-13.

With respect to restriction among groups I-IV, Applicants' traversal is on the grounds that each group of I through IV is defined as a "method for measuring IP3" and should be examined together. This is not found persuasive because each of the Inventions of group I-IV is unrelated to each other for the reasons of record on pages 2 in paragraph 2 Office Action of October 5, 2006. In addition, the search for each of the distinct inventions of Groups I-IV is not co-extensive particularly with regard to the literature search. Further, a reference that would anticipate the invention of one group would not necessarily anticipate or even make obvious another group. Finally, the condition for patentability is different in each case. Thus, it will be an undue burden to examine all the inventive Groups in one application. Therefore, the restriction requirement is still deemed proper and is made FINAL.

Accordingly, Claims 9-17 and 20-21 are withdrawn from further consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Examiner suggests that the non-elected claims cited supra be canceled in response to this Office action to expedite prosecution.

However, Applicants argument regarding search for "detectable label" is convincing and therefore, election of species requirement is hereby withdrawn.

Therefore, claims 1-8 and 18-19 are examined on merits.

Information Disclosure Statement

2. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP j 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim objections

3. Claim 1 is objected to because of the following informalities: Abbreviations "IP_3" and "IP_3R" in the claim is not proper. Applicant is suggested to spell out the abbreviation the first time it is used in the claim, so that the structure of the compound and or the name of the receptor are clearly defined. e.g. inositol 1,4,5-triphosphate (IP_3) and inositol 1,4,5-triphosphate receptor (IP_3R).

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Although specific claims may be discussed in the rejections below, these rejections are also applicable to all other claims in which the noted problems/language occur.
6. Claims 1-8 and 18-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
7. Claim 1 recites the phrase "a detectable label joined through a bond or linker at the 2-hydroxyl position". It is not clear whether the "2-hydroxyl position" is of the "inositol 1,4,5-triphosphate (IP_3)" or other compound. If it is IP_3, a phrase "of said IP3" should be inserted after "2-hydroxyl position" in order to clearly define the point of linkage.
8. Claim 1 lacks antecedent basis for the term "said binding protein" in lines 6-7.
9. The recitation "sufficient time" in line 7 of claims 1 is indefinite. It is not clear how one can determine with clarity and accuracy the length of time that is sufficient for any IP3 and said conjugate to bind to said binding proteins and a the length of time in a condition that is sufficient in one case, may not be sufficient for another. Applicant is advised to define the term "sufficient time".
10. Claim 1 recites the phrase "detecting the bound and unbound label as a measure of the IP_3 present in the sample" in lines 9-10. The step should be re-written to clearly indicate how "detecting the bound or unbound label" is correlated with the "measuring of IP_3".
11. Claim 3 recites the phrase "wherein said cellular lysate has been treated to block kinases and phosphatases". It is unclear cellular lysate is treated with "what" in order

to block kinases and phospatases i.e. the process by which kinases and phosphatases in said cellular lysate is blocked is unclear.

12. Claim 6 recites the phrase "wherein said binding protein is a fusion protein of up to about 1.5 kD amino acids". The nature and chemical structure of the fusion protein in unclear because its not clear what sequence or portion of the IP_3R is fused to "what" amino acid sequence or protein or peptide sequence.

13. The dependency of claim 18 and 19 should be corrected to properly make it dependent on an elected claims of 1-8 and should be re-written to include all the limitations of claim 1 or any intervening claims.

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-3 and 5-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for truncated extracellular portion of mouse Type1 IP_3R comprising at least amino acids sequence of 226-578, do not reasonably provide enablement for all any truncated portion (sequence) of IP_3R as binding protein which would have an affinity of at least about 200 times the affinity for IP_3 than that of intact IP_3R for IP_3.

The specification provides guidance and working examples for use of core protein or "sponge" derived from amino acid sequence 226-578 of type 1 mouse IP_3R1. But there is no enablement in the specification for use of <u>any</u> trancated portion (sequence) of IP_3R not containing the core sequence that provide high

binding (200 times that that of intact IP_3R) as required by claim 1. For IP_3 binding, conserved lysine and arginine residues in N-terminal 226-576 are important (Riley et al. Journal of Biological Chemistry 2002) and first N terminal 225 residues may in fact inhibit IP3 binding (Morris et al. Biochem J. 2002). Therefore, an artisan in the art would not be able to practice the invention because an undue experimentation will be required to judge suitability of any trancated extracellular portion of IP_3R as binding protein having binding affinity as described above. Undue experimentation would be required to practice the invention as claimed due to the quantity of experimentation necessary; limited amount of guidance and limited number of working examples in the specification; nature of the invention; state of the prior art; relative skill level of those in the art; predictability or unpredictability in the art; and breadth of the claims. In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 1-4, 6-8 and 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sportsman et al. (US 6,806,053 B1) in view of Iwasaki et al. (J. Biol. Chem. 2002) and Hirata et al. (J. Biol. Chem. 1990).

Sportsman et al. in a cell-signaling assay of inositos-phospholipid signaling pathway, disclose detection of intermediate 1,4, 5 IP_3 of the singnaling pathway. The assay include a tracer from the intermediate (i.e. tracer of 1,4, 5 IP_3) and a specific binding partner for 1,4,5 IP_3 (intermediate) and the tracer (e.g. labeled 1,4, 5 IP_3). Sportsman et al. also disclose that the tracer may include a luminophore attached by a suitable chemistry to the intermediate (e.g. a fluorescein succinyl-labeled IP_3)(column 20, example 14 and figs. 5 & 6).

Sportsman et al. disclose that specific binding partner generally comprises any compound capable of specifically and competitively binding an analyte and an associated tracer and also disclose that fragments, derivatives or analogs of a preferred specific binding partner may be used (column 11, lines 22-35). Sportsman et al., however, do not disclose IP_3R receptor or fragments thereof as specific binding partner in this assay.

Iwasaki et al. disclose IP_3R antagonists that strongly and specifically bind to IP_3 (analyte). Iwasake et al. also disclose N-terminal ligand binding domain of mIP_3R1 comprising amino acid sequence 226-578 as the core region for high affinity binding to IP_3 (see page 2764, left column, lines 6-18).

Since specific binding partner for IP_3 in common and known in the art (Iwasaki et al.), it would have been obvious at the time of the invention to a person of ordinary

skill in the art to include IP_3R receptor or truncated portion of the IP_3R as taught by Iwasaki et al in the assay method of Sportsman to effectively measure IP_3 in a sample with a reasonable expectation of success because specific binding partner for IP3 is envisaged in the method of Sportsman et al.

As for conjugate of IP_3 with a detectable label, Sportsman et al. disclose that the tracer may include a luminophore attached by a suitable chemistry to the intermediate (e.g. a fluorescein succinyl-labeled IP_3)(column 20, example 14) but, however, fail to disclose detectable label at the 2-hydroxy position of IP_3.

Hirata et al. disclose a series of 1,4,5-triphosphate (IP_3) analogs with substituents at 2 hydroxy position and disclose that such modification (substitution at 2-hydroxy position) do not substantially interfere with the affinity of IP_3 for IP_3 receptor (see abstrace and page 8404, right column, lines 6-13).

Therefore, given the above fact that substitution at the 2-hydoxyl position with bulky groups do not significantly alter binding affinity of IP_3 for its binding partner (Hirata et al.), it would have been obvious at the time of the invention to a person of ordinary skill in the art to attach luminophore at the 2-hydroxy position of IP_3 in the IP_3-luminophore conjugate of Sportsman et al with a reasonable expectation of success because attachment by a suitable chemistry is disclosed by Sportsman et al. and substitution at the position is preferable for not effecting IP3 binding affinity.

As for dependent claim 2, Sportsman et al. disclose that the assay may be homogeneous (column 9, lines 49-52). As for claims 4 and 6 Iwasaki disclose amino acid sequence 226-578 as the core region for high affinity binding to IP_3 and disclose

a fusion protein (IP3 sponge) (page 2764, left column, lines 6-18) and as for claims 18-19, Sportsman et al. disclose component in a kit format (column 13, lines 34-35) and the packaging of components in kit form is a well-known obvious expedient for ease and convenience in assay performance and once a method has been established, one skilled in the art would clearly consider compiling in a kit format and change/modify different components of the kit to best suit the assay.

18. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sportsman et al. (US 6,806,053 B1), Iwasaki et al. (J. Biol. Chem. 2002) and Hirata et al. (J. Biol. Chem. 1990) as applied to claims 1-4, 6-8 and 18-19 above and further in view of Henderson et al. (US 4708,929).

See above teaching for Sportsman et al., Iwasaki et al and Hirata et al in paragraph 17.

Sportsman et al. disclose IP3 conjugated with a label (e.g. luminophore) but remain silent about other labels (e.g. enzyme label).

Henderson et al. in a competitive assay for protein binding disclose labeling analyte with enzyme fragment (donor enzyme fragment e.g. enzyme donor of b-galactosidase) for detection by complementation with an enzyme acceptor that results in measurable enzyme activity (abstract and column 10, line 57 through column 11, line 32). Henderson et al. also disclose that enzyme complementation is advantageous over other immunoassays employing fluorescent label as fluorescent label analyte require separation steps and are limited to small molecular weight analytes .

Since labeling analytes with enzyme fragment (enzyme donor conjugate i.e. tracer) is common and know for its sensitive detection and are not limited to small molecular analytes (Henderson et al.), it would have been obvious to one of ordinary skill in the art at the time the invention was made to use enzyme fragment (e.g. donor fragment of beta-galactosidase) to label IP_3 in the method of Sportsman et al. for detection of analytes with a reasonable expectation of success because production of enzyme fragment label conjugate and complementation assays are taught in the method of Henderson et al.

Conclusion

19. The prior art made of record and not relied upon is considered pertiinent to applicant's disclosure.

Yoshikawa et al. (Biochem. Biophy. Res. Comm. 1999) disclose important region of binding domain of IP3 receptor for binding to IP3.

Riley et al. (J. Biol. Chem. 2002) disclose PEG linker at 2-hydroxyl position of IP3 more potent than IP3.

Morris et al. (Biochem. J. 2002) disclose that IP3 binding site lies within the N-terminal between residues 226 and 576 and the first 225 residues may inhibit IP3 binding.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shafiqul Haq whose telephone number is 571-272-6103. The examiner can normally be reached on 7:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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